REMARKS

This Amendment, filed in reply to the Office Action dated April 30, 2008, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1-42 are all the claims pending in the application. Claims 1-23 are withdrawn from consideration as being directed to non-elected inventions. Claims 24-42 are rejected. Claim 24 is amended herewith to incorporate the subject matter of Claims 25 and 29. Claim 33 is amended herewith to provide proper antecedent basis in view of the amendment to Claim 24. Claims 25, 28, 29 and 39 are canceled herewith without prejudice or disclaimer.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Claim to Priority

Applicants thank the Examiner for acknowledging Applicants' claim to foreign priority, and receipt of all the priority documents.

Information Disclosure Statement

Applicants thank the Examiner for returning a signed and initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed March 18, 2005, indicating consideration of the references therein.

Objections to the Specification

On page 2 of the Office Action, the Examiner asserts that the title of the invention is not sufficiently descriptive. The Examiner requests that a new title, clearly indicative of the claimed invention, be submitted. Specifically, the Examiner suggests that amending the title to recite "Stabilized Vaccine Compositions and Methods" may obviate the objection.

Solely to advance prosecution, and without agreeing with the objection, Applicants herewith amend the title in accordance with the Examiner's suggestion, obviating the objection.

Withdrawal of the objection is respectfully requested.

Objections to the Claims

On page 2 of the Office Action, the Examiner objects to Claim 39 as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Solely to advance prosecution, and without acquiescing in the objection, Applicants note that Claim 39 is canceled herewith without prejudice or disclaimer, mooting the objection.

Withdrawal of the objection is respectfully requested.

Claims 24, 26, 27, 30-38 and 40-42 are Patentable Under 35 U.S.C. § 103

1. On page 3 of the Office Action, the Examiner rejects Claims 24-28, 30-36 and 38 under 35 U.S.C. § 103(a) as obvious over Jameela *et al.*

In making the rejection, the Examiner asserts that Jameela *et al.* disclose immunogenic compositions comprising chitosan microspheres coated with diptheria toxoid (DT) and bovine serum albumin (BSA). The Examiner asserts that the explicit teachings of Jameela *et al.* encompass the limitations of Claims 24-28, 30-36 and 38. Nevertheless, the Examiner also takes

the position that one of ordinary skill in the art would readily have arrived at the claimed moisture content and particle size, because one of ordinary skill in the art "would have recognized particle size and moisture content as result effective variables," citing Desai *et al.* and Precausta *et al.*, respectively, and thus would have been motivated to optimize such variables for vaccine development.

Applicants respectfully disagree, and traverse the rejection on the following grounds.

First, Applicants note that Claim 24 has been amended to incorporate the limitations of Claims 25 and 29. Claim 24 as amended is not obvious over Jameela *et al.* at least because Jameela *et al.* fail to disclose that the immunogen comprises virus particles, bacterial cells or other microorganisms, or that the composition is stable and efficacious on storage at 25°C for 30 days. Jameela *et al.* only disclose diphtheria toxoid (DT)-coated microspheres. DT is an isolated *protein*, not a virus particle, bacterial cell or other microorganism. Accordingly, Jameela *et al.* do not teach each and every element of the claims, as is required to maintain a finding of obviousness. Further, the technical considerations for making stable compositions of purified proteins vis-à-vis whole microorganisms such as viruses and bacteria are entirely different, and thus Jameela *et al.* cannot render obvious the claimed composition for this reason also. As would be appreciated by one of ordinary skill in the art, whole microorganisms are considerably more complex than single proteins, and thus the skilled artisan would not look to Jameela *et al.* to arrive at a composition for stabilization of whole microorganisms.

Further, Jameela *et al.* do not disclose a composition having a moisture content "between about 0.1% w/w to about 10% w/w," as claimed. Rather, Jameela *et al.* are silent as to the moisture content of the composition.

Although the Examiner takes the position that moisture content is a result effective variable, citing Precausta *et al.* as support, Applicants note that Precausta *et al.* do not establish moisture content as a result-effective variable in vaccine compositions comprising *immunogen-coated particles*, and thus does not serve to support a finding of obviousness. To the contrary, the disclosure of Precausta *et al.* is directed solely to freeze-dried compositions. Precausta *et al.* are entirely silent as to whether moisture content affects the stability of *any* other type of vaccine composition, much less vaccine compositions comprising immunogen-coated particles containing microorganisms.

Furthermore, one of ordinary skill in the art would understand Jameela *et al.* to disclose that such microspheres allow for extended release of DT *in vivo*, that is, in an aqueous environment. Jameela *et al.* neither teach nor even suggest whether such microspheres may be useful for stabilizing vaccine compositions in a dried state, much less whether moisture content is an important factor for stability in such a dried state. Because Precausta *et al.* is directed to freeze-dried compositions lacking microspheres, Precausta *et al.* also says nothing as to whether moisture content has any effect on the stability of vaccine compositions containing immunogen-coated particles, such that one of ordinary skill in the art would consider moisture content of compositions containing immunogen-coated particles to be a result-effective variable. Before a determination of the optimum or workable ranges of a variable can be characterized as routine experimentation, the variable must first be recognized as a variable which achieves a recognized result. See *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). Precausta *et al.* say nothing as to whether moisture content is a result-effective variable in compositions containing immunogen-coated particles, such that the optimum or workable ranges of this variable can be

considered routine experimentation. For this reason also, a *prima facie* case of obviousness has not been established.

Further still, independent of the above arguments, Applicants submit that one of ordinary skill in the art would have no motivation nor reason to modify the moisture content of the composition of Jameela *et al.*, because the composition of Jameela *et al.* comprises cross-linked chitosan microspheres as a long-acting drug delivery vehicle *in vivo*. At no point do Jameela *et al.* even suggest freeze-drying the composition such that moisture content would be a consideration. To the contrary, Jameela *et al.* is directed to increasing the stability of antigens *in vivo* (*i.e.*, in an aqueous environment) by conjugation to microspheres, and therefore one of ordinary skill in the art would have no motivation to reduce the moisture content of the composition. Indeed, in the abstract, Jameela *et al.* suggest that high moisture content is important for the composition, by stating that "[i]t is also shown that drugs passively absorbed into such matrices by taking advantage of their swelling behavior need not necessarily be released completely in the initial 'burst' and a sustained release may be possible for macromolecules thus incorporated." (Emphasis added.)

Accordingly, one of ordinary skill in the art would instantly realize that the composition of Jameela *et al.* depends on swelling of the microspheres in solvent for passively absorbing DT, thus teaching away from producing essentially a dried composition having a moisture content of "between about 0.1% w/w to about 10% w/w." Furthermore, Jameela *et al.* is entirely silent as to whether such microspheres have any stabilizing effect in a low moisture state.

For the foregoing reasons, Applicants submit that a *prima facie* case of obviousness has not been established.

Withdrawal of the rejection is respectfully requested.

2. On page 4 of the Office Action, Claim 29 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Jameela *et al.* in view of Chang and Gupta.

Jameela *et al.* is relied upon for the same reasons as in the rejection of Claims 24-28, 30-36 and 38. However, the Examiner acknowledges that Jameela *et al.* do not disclose that the composition is efficacious after storage at 25°C for at least 30 days. In an attempt to rectify the deficiencies of Jameela *et al.*, the Examiner cites to Chang and Gupta, who allegedly disclose a vaccine composition that is stable for 30 days at 25°C. The Examiner contends that gelatin appears to be the factor most closely correlated with stability and could easily be incorporated into the composition of Jameela *et al.* to extend stability.

Applicants respectfully disagree, and traverse the rejection on the following grounds.

Initially, Applicants note that Claim 29 is cancelled herewith, mooting the rejection. Nevertheless, in the interest of compacting prosecution, Applicants address the rejection as it applies to Claim 24 as amended, and claims dependent therefrom.

First, Applicants submit that the instant claims are not rendered obvious for the same reasons presented above, namely that the cited references do not disclose an immunogen comprising virus particles, bacterial cells or other microorganisms. As discussed above, Jameela *et al.* only disclose diphtheria toxoid (DT)-coated microspheres. DT is an isolated *protein*, not a virus particle, bacterial cell or other microorganism. This deficiency is not rectified by the addition of Chang and Gupta, since Chang and Gupta only disclose tetanus toxoid-coated PLGA microspheres. Again, tetanus toxoid is an isolated *protein*. Thus, neither Jameela *et al.* nor Chang and Gupta, taken alone or in combination, teach each and every element of the claims, as is required to maintain a finding of obviousness.

Further, neither Jameela *et al.* nor Chang and Gupta disclose a composition having a moisture content "between about 0.1% w/w to about 10% w/w," as claimed. Thus, the cited references fail to teach each and every element of the claims for this reason also. Such is not a result-effective variable, as asserted in the Office Action, for the same reasons discussed above.

In addition, Applicants respectfully submit that one of ordinary skill in the art would have no motivation nor reason to add gelatin to an essentially dried composition, as claimed, because Chang and Gupta only suggest that gelatin may have a stabilizing effect in an aqueous environment *in vitro*. Chang and Gupta are silent as to whether gelatin has any effect on the stability of such vaccine compositions in a dried state.

For the foregoing reasons, a *prima facie* case of obviousness has not been established.

Withdrawal of the rejection is respectfully requested.

3. On page 5 of the Office Action, Claim 37 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Jameela *et al.* in view of Spireas *et al.*

Jameela *et al.* is relied upon for those same reasons as in the rejection of Claims 24-28, 30-36 and 38. The Examiner acknowledges that Jameela *et al.* do not disclose that the composition is a free flowing particulate composition. In an attempt to rectify the deficiencies of Jameela *et al.*, the Examiner cites to Spireas *et al.*, who allegedly disclose methods for making compositions of "free flowing particulates." The Examiner contends that a skilled artisan would have been motivated to combine the methods of Jameela *et al.* and Spireas *et al.* to take advantage of the delivery properties of free flowing particulates.

Applicants respectfully disagree, and traverse the rejection on the following grounds.

Initially, Applicants note that Spireas *et al.* do not compensate for the deficiencies of Jameela *et al.*, discussed above. Specifically, Spireas *et al.* do not disclose a composition containing an immunogen comprising virus particles, bacterial cells or other microorganisms, or that the composition has a moisture content of between about 0.1% w/w to about 10% w/w. Accordingly, neither Jameela *et al.* nor Spireas *et al.*, taken alone or in combination, teach each and every element of the claims, as is required to maintain a finding of obviousness. In addition to the above, Applicants submit that one of ordinary skill in the art would not reasonably combine Spireas *et al.* with Jameela *et al.*, because Spireas *et al.* is directed solely to theoretical models for formulating powered solutions of drugs, and provides no guidance as to the production of free flowing particulate compositions containing any biological, much less one containing microorganisms.

For the foregoing reasons, a *prima facie* case of obviousness cannot be established.

Withdrawal of the rejection is respectfully requested.

4. On page 5 of the Office Action, Claims 40-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Jameela *et al.* in view of Villegas *et al.*, Macklin *et al.* and Layton *et al.*

In making the rejection, the Examiner contends that given the relatively limited number of approved vaccine targets, it would have been obvious at the time of the invention for one of ordinary skill in the art to combine the teachings of Jameela *et al.*, Villegas *et al.*, Macklin *et al.* and Layton *et al.* to construct the claimed vaccine composition. The Examiner contends that one of ordinary skill in the art would have had a reasonable expectation of success considering the

immunogenicity of the antigens taught by Villegas *et al.*, Macklin *et al.* and Layton *et al.*, and the robustness of the particles of Jameela *et al.* in inducing an immune response.

Applicants respectfully disagree, and traverse the rejection on the following grounds.

Initially, Applicants note that the addition of Villegas *et al.*, Macklin *et al.* and Layton *et al.* does not compensate for the deficiencies of Jameela *et al.*, which are discussed above. Specifically, neither Villegas *et al.*, Macklin *et al.* nor Layton *et al.* disclose a composition containing immunogen coated particles, wherein the immunogen comprises virus particles, bacterial cells or other microorganisms, or that the composition has a moisture content of between about 0.1% w/w to about 10% w/w.

Specifically, Villegas *et al.* only disclose aerosolized Newcastle Disease Virus, which does not contain any coating particle, but rather, a dispersion medium, *i.e.*, a gas, and Newcastle Disease Virus. However, the instant claims recite immunogen-coated particles. Macklin *et al.* only disclose DNA-coated microparticles, not microparticles coated with any microorganism. Layton *et al.* only disclose virus-like particles (VLPs) carrying peptides. As would be appreciated by one of ordinary skill in the art, VLPs are not a water-soluble material, as claimed, but rather are maintained in suspension. Further, as discussed above, peptides are not whole microorganisms.

Accordingly, neither Jameela *et al.*, Villegas *et al.*, Macklin *et al.* nor Layton *et al.*, taken alone or in combination, teach each and every element of the claims, as is required to maintain a finding of obviousness.

In addition to the above, Applicants respectfully disagree with the Examiner's reasoning that one of ordinary skill in the art would readily employ the composition of Jameela *et al.* to produce a vaccine composition using the antigens of Villegas *et al.*, Macklin *et al.* and Layton *et*

al. because of the robustness of the particles of Jameela *et al.* in inducing an immune response. To the contrary, Jameela *et al.* actually teach away from such a composition, because in the abstract, Jameela *et al.* state that "[p]reliminary immunogenicity studies on Wistar rats using DT loaded chitosan spheres showed that the antibody titres were fairly constant over a 5-month period, although **very low** compared to DT given on alum as control." Emphasis added. Accordingly, one of ordinary skill in the art would instantly realize from Jameela *et al.* that the microspheres of Jameela *et al.* are a poor means for vaccine delivery, and that using simple alum adjuvant, which is routinely used in the art, is significantly more effective. For this reason, the cited references teach away from combining Jameela *et al.* with Villegas *et al.*, Macklin *et al.* and Layton *et al.*

For the foregoing reasons, a *prima facie* case of obviousness has not been established.

Withdrawal of the rejection is respectfully requested.

Double Patenting

On page 7 of the Office Action, Claims 24-26, 28, 30-31, 33-36, and 38 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1, 3, 4, 6, and 10 of U.S. Patent No. 6,974,594.

Applicants note that the subject matter of Claim 29, which has not been rejected over the '594 Patent, has been incorporated into Claim 24, mooting the rejection.

Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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